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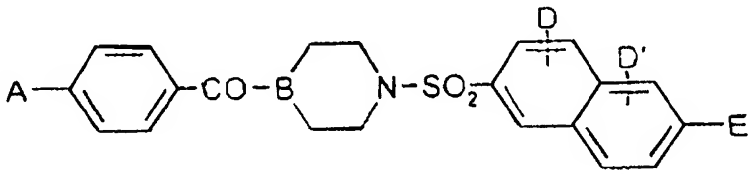

(I)

(57) Abstract

The invention relates to heterocyclic derivatives of formula (I), or pharmaceutically–acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparatiion of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.

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HETEROCYCLIC DERIVATIVES WHICH INHIBIT FACTOR XA

The invention relates to heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.

The antithrombotic and anticoagulant effect produced by the compounds of the invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by R.B. Wallis, Current Opinion in Therapeutic Patents, 1993, 1173-1179. Thus it is known that two proteins, one known as antistatin and the other known as tick anticoagulant protein (TAP), are specific Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by R.B. Wallis, all possessed a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

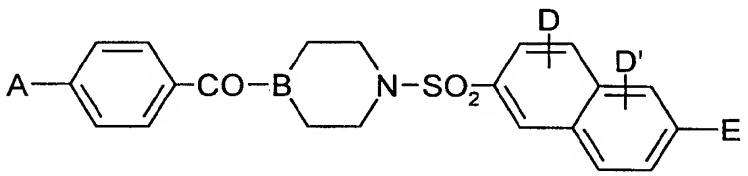
We have now found that certain heterocyclic derivatives possess Factor Xa inhibitory activity. Many of the compounds of the present invention also possess the advantage of being selective Factor Xa inhibitors, that is the enzyme Factor Xa is inhibited strongly at concentrations of test compound which do not inhibit or which inhibit to a lesser extent the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

The compounds of the present invention possess activity in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated, for example in the treatment or prevention of thrombotic conditions such as coronary artery and

cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular injury including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischaemia and angina (including unstable angina).

The compounds of the invention are also useful as inhibitors of blood coagulation in an ex-vivo situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

Accordingly in one aspect the present invention provides compounds of formula (I)



(I)

wherein:

A is a 5- or 6-membered monocyclic aromatic ring containing 1 or 2 nitrogen ring heteroatoms optionally substituted by one, two or three atoms or groups selected from halo (for example fluoro, chloro or bromo), oxo, carboxy, trifluoromethyl, cyano, amino, hydroxy, nitro, C_{1-4}alkyl (for example methyl or ethyl), C_{1-4}alkoxy (for example methoxy or ethoxy), C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino (for example methylamino or ethylamino), di-C_{1-4}alkylamino (for example dimethylamino or diethylamino) or aminoC_{1-4}alkyl (for example aminomethyl or aminoethyl);

the 1,4-phenylene ring of the compound of formula I is unsubstituted or is substituted by one or two substituents selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl, from the substituent $-(CH_2)_n Y^1$ wherein n is 0-4 and Y^1 is selected from hydroxy, amino, carboxy, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy,

C_{1-4}alkylamino, di-C_{1-4}alkylamino, pyrrolid-1-yl, piperidino, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-C_{1-4}alkylpiperazin-1-yl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, C_{2-4}alkanoylamino, benzamido, C_{1-4}alkylsulphonamido and phenylsulphonamido, from the substituent $-(CH_2)_nY^2$ wherein n is 0-4 and Y^2 is selected from carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl, N,N-di-C_{1-4}alkylcarbamoyl, pyrrolid-1-ylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, 1-oxothiomorpholinocarbonyl, 1,1-dioxothiomorpholinocarbonyl, piperazin-1-ylcarbonyl, 4-C_{1-4}alkylpiperazin-1-ylcarbonyl, C_{1-4}alkylsulphonamidocarbonyl, phenylsulphonamidocarbonyl and benzylsulphonamidocarbonyl, from a substituent of the formula $-X^3-L^2-Y^2$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^2-Y^2)$, $C(R^5)_2O$, O, $N(R^5)$ or $N(L^2-Y^2)$, L^2 is C_{1-4}alkylene, Y^2 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and from a substituent of the formula $-X^3-L^3-Y^1$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^3-Y^1)$, $C(R^5)_2O$, O, $N(R^5)$ or $N(L^3-Y^1)$, L^3 is C_{2-4}alkylene, Y^1 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and wherein any heterocyclic group in a substituent of the 1,4-phenylene ring of compounds of formula I optionally bears 1 or 2 substituents selected from carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl and N,N-di-C_{1-4}alkylcarbamoyl, and wherein any phenyl group in a substituent of the 1,4-phenylene ring of compounds of formula I optionally bears 1 or 2 substituents selected from halo, trifluoromethyl, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy and C_{2-4}alkynyloxy;

B is CH or N;

the heterocyclic ring containing B is unsubstituted or is substituted by one or two substituents selected from hydroxy, oxo, carboxy and C_{1-4}alkoxycarbonyl; or one of the following:

$-(CH_2)_n-R$, $-(CH_2)_n-NRR^1$, $-CO-R$, $-CO-NRR^1$, $-(CH_2)_n-CO-R$ and $-(CH_2)_n-CO-NRR^1$;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R and R^1 are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl or where possible R and R^1 may together form a 5- or 6-membered optionally substituted saturated or partially unsaturated (preferably saturated) heterocyclic ring which may include in addition to the nitrogen to which R and R^1 are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur;

E is fluoro, chloro or bromo;

D and D^1 are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, oxo and hydroxy;

provided that when E is bromo and B is N then A is not 2-pyridyl, 4-pyridyl, 4-pyrimidinyl or 4-pyridazinyl, and when E is chloro and B is N then A is not 3-pyridyl, 4-pyridyl or 4-pyrimidinyl;

and pharmaceutically acceptable salts thereof.

It is to be understood that certain heterocyclic derivatives of the present invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Factor Xa inhibitory activity.

It is further to be understood that, insofar as certain of the compounds of formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which possesses Factor Xa inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Preferably A is an optionally substituted pyrrolyl, imidazolyl or pyridazinyl ring, for example; 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl; 1-imidazolyl, 2-imidazolyl or 4-imidazolyl; 1-pyridazinyl, 3-pyridazinyl or 4-pyridazinyl. Of these 3-pyridazinyl, 1-imidazolyl and 4-imidazolyl are preferred of which 1-imidazolyl and 4-imidazolyl are most preferred.

For the avoidance "oxo" as used herein defines the substituent "=O". For the avoidance of doubt substituents on A may also be present, where possible, on the heteroatom of the ring, such as, for example, N-oxides.

Preferred substituents of A are C_{1-4}alkyl, amino and halo. Preferably A is unsubstituted.

Preferably the 1,4-phenylene ring of a compound of formula I is substituted by carboxy, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl. Preferably the 1,4-phenylene ring of a compound of formula I is unsubstituted.

In a particular aspect the heterocyclic ring formed by R and R^1 present on a substituent of the heterocyclic ring containing B is preferably selected from 1-pyrrolidyl, 1-imidazolyl, 1-piperidino, 1-piperazinyl, 4-morpholino and 4-thiomorpholino. In a particular aspect the heterocyclic ring formed by R and R^1 may be unsubstituted . In an alternative aspect the ring formed by R and R^1 is substituted by 1 or 2 substituents selected from oxo, hydroxy and carboxy. Preferably the heterocyclic ring containing B is substituted by oxo, carboxy, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl. Preferably the heterocyclic ring containing B is unsubstituted.

Suitable values for optional substituents for the 1,4-phenylene ring of compounds of formula I are:

for C_{1-4}alkyl:	methyl, ethyl and propyl;
for C_{1-4}alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-C_{1-4}alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-C_{1-4}alkylcarbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for hydroxyC_{1-4}alkyl:	hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl;
for C_{1-4}alkoxyC_{1-4}alkyl:	methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for carboxyC_{1-4}alkyl:	carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;
for C_{1-4}alkoxycarbonylC_{1-4}alkyl:	methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxy-carbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl;
for carbamoylC_{1-4}alkyl:	carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;
for N-C_{1-4}alkylcarbamoylC_{1-4}alkyl:	N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;
for N,N-di-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl:	N,N-dimethylcarbamoylmethyl, N-ethyl-N-methylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, 1-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-diethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 2-(N,N-diethylcarbamoyl)ethyl and 3-(N,N-dimethylcarbamoyl)propyl;
for halo:	fluoro, chloro, bromo;

for C_{1-4}alkoxy:	methoxy, ethoxy;
for C_{1-4}alkylamino:	methylamino, ethylamino;
for di-C_{1-4}alkylamino:	dimethylamino, diethylamino;
for C_{1-4}alkenyl:	vinyl and allyl;
for C_{2-4}alkynyl:	ethynyl and prop-2-ynyl;
for C_{2-4}alkenyloxy:	vinyloxy and allyloxy;
for C_{2-4}alkynyloxy:	ethynyloxy and prop-2-ynyloxy;
for C_{1-4}alkylthio:	methylthio, ethylthio and propylthio;
for C_{1-4}alkylsulphinyl:	methylsulphinyl, ethylsulphinyl and propylsulphinyl;
for C_{1-4}alkylsulphonyl:	methylsulphonyl, ethylsulphonyl and propylsulphonyl;
for C_{2-4}alkanoylamino:	acetamido, propionamido and butyramido;

A preferred class of compounds of formula (I) are those wherein:

A is imidazolyl;

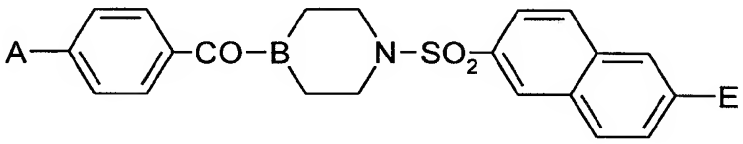
B is N;

E is chloro or bromo;

D and D^1 are both hydrogen.;

and pharmaceutically-acceptable salts thereof.

Additional compounds of the invention include compounds of formula(Ia):



wherein:

A is phenyl, pyrimidinyl (preferably 4-pyrimidinyl) or pyridyl (preferably 4-pyridyl) substituted (preferably at position 2- or 5-, in particular 5-, on the pyrimidinyl or pyridyl, and preferably at position 3- for phenyl) by one or two substituents selected from:

R^1-$(CH_2)_{1\text{ to }3}$-, RRN-$(CH_2)_{1\text{ to }3}$-, R-CO-, RRN-CO-, R-CO-$(CH_2)_n$-, RRN-CO-$(CH_2)_n$-, RRN-CO-RRN-$(CH_2)_n$-, RRN-RRN-$(CH_2)_n$- and R-O-$(CH_2)_n$-;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R is independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, N,N-di-C_{1-4}alkylaminoC_{1-4}alkyl;

R^1 is independently selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, N,N-di-C_{1-4}alkylaminoC_{1-4}alkyl;

B is CH or N (preferably B is N);

D is bromo or chloro:

and pharmaceutically acceptable salts thereof.

Preferred for A in compounds of formula (Ia) are 4-pyrimidinyl and 4-pyridyl.

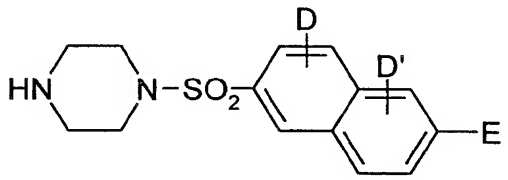
Particular compounds of the invention include the specific compounds disclosed in the Examples.

A heterocyclic derivative of the formula (I) or (Ia), or pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of related compounds. Such procedures are provided as a further feature of the invention and are illustrated by the following representative processes in which, unless otherwise stated A, B, E, D and D^1 have any of the meanings defined hereinbefore wherein any functional group, for example amino, alkylamino, carboxy or hydroxy, is optionally protected by a protecting group which may be removed when necessary.

Necessary starting materials may be obtained by standard procedures of organic chemistry and by reference to the processes used in the Examples.

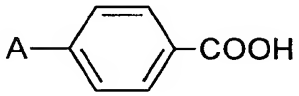
According to another aspect, the present invention provides a process for preparing a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt thereof, which comprises:

(a) For the production of those compounds of the formula (I) or (Ia) wherein B is N, the reaction, conveniently in the presence of a suitable base, of an amine of formula (II)



(II)

with an acid of the formula (III)



(III)

or a reactive derivative thereof.

A suitable reactive derivative of an acid of the formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated amide such as 1,1'-carbonyldiimidazole; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole or N-hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide.

The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably

carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

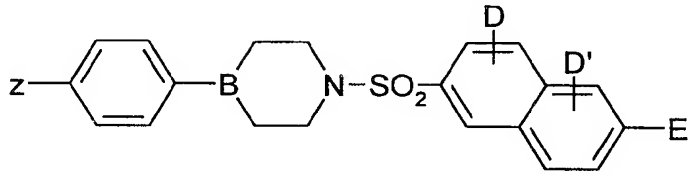
A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric, phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. An arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by

hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

(b) The reaction of a compound of the formula (IV):



(IV)

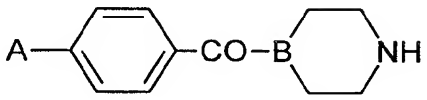
wherein Z is a displaceable group such as halo, with an activated derivative of ring A. Suitable activated derivatives include metalised derivatives, such as with zinc or tin, and borane derivatives. The activated derivative of ring A is reacted with a compound of the formula (IV) to effect cross coupling where Z is triflate or a halo group, such as iodo, bromo or chloro. Suitably the reaction is catalysed by use of a transition state metal catalyst, such as palladium, for example tetrakis (triphenylphosphine) palladium (0).

Alternatively it is possible that ring A contains the displaceable group Z and the phenyl ring is activated, and the reaction performed as described above.

Compounds of the formula (IV) not suitable for this method are those which contain a halo substituent on any of the rings.

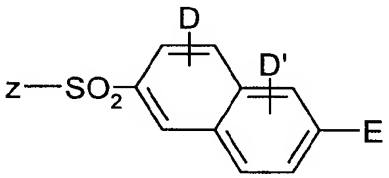
(c) By forming A ring on compounds of formula (IV), wherein Z is a functional group capable of cyclisation. Suitable reagents and conditions are described below in preparing compounds of formula (III) by cyclisation. Suitable reagents and conditions are described in Bredereck H. Chem.Ber.; 96, 1505, (1963); Fuchigami, T., Bull. Chem. Soc. Jpn., 49, p3607, (1976); Huffman, K.R., J. Org. Chem., 28, p1812, (1963); Palusso, G., Gazz. Chim. Ital., 90, p1290, (1960) and Ainsworth C.J., Heterocycl. Chem., 3, p470, (1966). Such reactions are particularly suited to the formation of 5-membered A rings. Processes suitable for synthesis of starting materials in such cyclisation reactions are described, for example, in Zhang M.Q. et.al; J.Heterocyclic. Chem.; 28, 673, (1991) and Kosugi, M. et al., Bull. Chem. Soc. Jpn., 60, 767-768 (1987).

(d) The reaction of a compound of the formula (V):



(V)

with a compound of the formula (VI):



(VI)

wherein Z is a displaceable group for example chloro, under conditions similar to those of process (a) above.

When a pharmaceutically-acceptable salt of a compound of the formula (I) is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure.

When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure, for example by the formation of diastereomeric salts, use of chromatographic techniques, conversion using chirally specific enzymatic processes, or by addition of temporary extra chiral group to aid separation.

As stated previously, the compounds of the formula (I) are inhibitors of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or more of the standard procedures set out hereinafter:-

a) Measurement of Factor Xa Inhibition

An in vitro assay system based on the method of Kettner et al., J. Biol. Chem., 1990, 265, 18289-18297, whereby various concentrations of a test compound are dissolved in a pH7.5 buffer containing 0.5% of a polyethylene glycol (PEG 6000) and incubated at 37°C with human Factor Xa (0.001 Units/ml, 0.3 ml) for 15 minutes. The chromogenic substrate S-2765 (KabiVitrum AB, 20 μM) is added and the mixture is incubated at 37°C for 20 minutes whilst the absorbance at 405 nm is measured. The maximum reaction velocity

(Vmax) is determined and compared with that of a control sample containing no test compound. Inhibitor potency is expressed as an IC_{50} value.

b) Measurement of Thrombin Inhibition

The procedure of method a) is repeated except that human thrombin (0.005 Units/ml) and the chromogenic substrate S-2238 (KabiVitrum AB, 7 μM) are employed.

c) Measurement of Anticoagulant Activity

An in vitro assay whereby human, rat or rabbit venous blood is collected and added directly to a sodium citrate solution (3.2 g/100 ml, 9 parts blood to 1 part citrate solution). Blood plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at 2-4°C. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to double the clotting time, hereinafter referred to as CT2, is determined. In the PT test, the test compound and blood plasma are incubated at 37°C for 10 minutes. Tissue thromboplastin with calcium (Sigma Limited, Poole, England) is added and fibrin formation and the time required for a clot to form are determined.

d) Rat Disseminated Intravascular Coagulation in vivo activity test:

Fasted male Alderley Park rats (300-450 g) are pre-dosed by oral gavage (5 mls/kg) with compound or vehicle (5% DMSO/PEG200) at various times before being anaesthetised with Intraval® (120 mg/kg i.p.). The left jugular vein and the right carotid artery are exposed and cannulated. A 1 mL blood sample is taken from the carotid canular into 3.2% trisodium citrate. 0.5 mL of the whole blood is then treated with EDTA and used for platelet count determination whilst the remainder is centrifuged (5 mins, 20000g) and the resultant plasma frozen for subsequent drug level, fibrinogen or thrombin antithrombin (TAT) complex determinations. Recombinant human tissue factor (Dade Innovin Cat.B4212-50), reconstituted to the manufacturers specification, is infused (2 mL/kg/hr) into the venous canular for 60 minutes. Immediately after the infusion is stopped a 2 mL blood sample is taken and platelet count, drug level, plasma fibrinogen concentration and TAT complex are determined as before. Platelet counting is performed using at Coulter T540 blood analyser. Plasma fibrinogen and TAT levels are determining using a clotting assay (Sigma Cat.880-B) and TAT ELISA (Behring) respectively. The plasma concentration of the compound is bioassayed using human Factor Xa and a chromogenic substrate S2765 (Kabi), extrapolated from a

standard curve (Fragmin) and expressed in Anti-Factor Xa units. The data is analysed as follows; tissue factor-induced reductions in platelet count are normalised with respect to pre-dose platelet count and drug activity expressed as a percent inhibition of tissue factor-induced thrombocytopenia when compared to vehicle treated animals. Compounds are active if there is statistically significant ($p < 0.05$) inhibition of TF-induced thrombocytopenia.

e) An ex vivo Assay of Anticoagulant Activity

The test compound is administered intravenously or orally to a group of Alderley Park Wistar rats. At various times thereafter animals are anaesthetised, blood is collected and PT coagulation assays analogous to those described hereinbefore are conducted.

f) An in vivo Measurement of Antithrombotic Activity

Thrombus formation is induced using an analogous method to that described by Vogel et al., Thromb. Research, 1989, 54, 399-410. A group of Alderley Park Wistar rats is anaesthetised and surgery is performed to expose the vena cava. Collateral veins are ligated and two loose sutures are located, 0.7 cm apart, round the inferior vena cava. Test compound is administered intravenously or orally. At an appropriate time thereafter tissue thromboplastin (30 µl/kg) is administered via the jugular vein and, after 10 seconds, the two sutures are tightened to induce stasis within the ligated portion of vena cava. After 10 minutes the ligated tissue is excised and the thrombus therein is isolated, blotted and weighed.

In general compounds of the formula I possess activity at the following concentrations or doses in at least one of the above tests a) to c):-

test a): IC_{50} (Factor Xa) in the range, for example, 0.001-0.1 µM;

test b): IC_{50} (thrombin), for example, greater than 40 µM;

test c): CT2 (PT) in the range, for example, 0.1-40 µM.

A feature of the invention is a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a heterocyclic derivative of formula (I) or (Ia), or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a heterocyclic derivative of the formula (I) or (Ia), or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided a heterocyclic derivative of formula (I) or (Ia), or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes the use of such an active ingredient in the production of a medicament for use in:-

(i) producing a Factor Xa inhibitory effect;

(ii) producing an anticoagulant effect;

(iii) producing an antithrombotic effect;

(iv) treating a Factor Xa mediated disease or medical condition;

(v) treating a thrombosis mediated disease or medical condition;

(vi) treating coagulation disorders; and/or

(vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of an active ingredient as defined hereinbefore.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the formula (I) are useful in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated. In using a compound of the formula (I) for such a purpose, it will generally be administered so that a daily oral dose in the range, for example, 0.5 to 100 mg/kg body weight/day is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed, for example a dose for intravenous administration in the range, for example, 0.01 to 10 mg/kg body weight/day will generally be used. For preferred and especially preferred compounds of the invention, in general, lower doses will be employed, for example a daily dose in the range, for example, 0.1 to 10 mg/kg body weight/day. In general a preferred dose range for either oral or parenteral administration would be 0.01 to 10 mg/kg body weight/day.

Although the compounds of formula (I) are primarily of value as therapeutic or prophylactic agents for use in warm-blooded animals including man, they are also useful whenever it is required to produce an anticoagulant effect, for example during the ex-vivo storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

The compounds of the invention may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

The invention will now be illustrated in the following Examples in which, unless otherwise stated:-

(i) yields are given for illustration only and are not necessarily the maximum attainable;

(ii) the end-products have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; unless otherwise stated, CD_3SOCD_3 solutions of the end-products of the formula I were used for the determination of NMR spectral data, chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet;

(iii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis; and

(iv) melting points were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the formula I were generally determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture.

Example 1

1-(6-Chloronaphth-2-ylsulphonyl)-4-[4-(4-imidazolyl)benzoyl]piperazine

To a solution of 4-(4-imidazolyl)benzoic acid hydrochloride (225mg, 1 mmol) in dimethylformamide (6ml) was added 1-(6-chloronaphth-2-ylsulphonyl) piperazine (311mg, 1 mmol), triethylamine (0.14 ml, 1 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride (EDAC, 230mg, 1.2 mmol), and the resultant suspension stirred overnight at ambient temperature. The solvent was removed *in vacuo*, the residue treated with water (15 ml) and the precipitated solid filtered off and washed with water to give 390mg of colourless solid.

This was purified by flash chromatography using Merck 9385 silica, eluting with dichloromethane containing methanol (7%), giving essentially pure product. This was crystallised from ethanol/hexane to give 1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(2-imidazolyl)benzoyl]piperazine (339 mg, 70% yield), m.p. 159-161 °C, ^{1}H NMR (d_6DMSO) 3.0-3.1 ppm (broad s,4H), 3.5-3.6 ppm (broad s,4H), 7.3ppm (d,2H), 7.6-7.9 ppm (m,6H), 8.2

ppm (d,1H), 8.3 ppm (d,2H), 8.5 ppm (s,1H), the spectrum also contained signals due to ethanol (1 mol eq.); microanalysis, found: C, 58.6; H, 5.1; N, 10.3 %; $C_{24}H_{21}N_4O_3ClS$. 1.0 C_2H_6O. 0.25 H_2O requires: C, 58.8; H, 5.2; N, 10.5 %; MS $(M+H)^+$ 481/483.

The requisite 4-(4-imidazolyl)benzoic acid starting material was prepared as follows. 4-(4-Imidazolyl)benzonitrile (507 mg, 3.0 mmol) was dissolved in hydrochloric acid (3 ml of 6M) and the mixture stirred at reflux overnight. The precipitate so formed was isolated by filtration, washed with 6M hydrochloric acid and dried to yield 4-(4-imidazolyl)benzoic acid hydrochloride (576 mg, 85% yield), ^{1}H NMR (d_6DMSO) 8.0 ppm (m,4H), 8.3 ppm (s,1H), 9.2 ppm (s,1H); MS $(M+H)^+$ 189.

The requisite 4-(4-imidazolyl)benzonitrile starting material was prepared as follows. 4-Cyanophenacyl bromide (2.24g, 10 mmol) was stirred at 210 °C in formamide (15 ml) for 2 hours. The reaction mixture was cooled and poured into water; this was basified and extracted with ethyl acetate (4x50 ml) to give crude product (1.4 g). This was purified by flash chromatography using Merck 9385 silica, eluting with ethyl acetate containing methanol (7.5%), giving essentially pure product. This was crystallised from ethyl acetate/hexane to give 4-(4-imidazolyl)benzonitrile (932 mg, 55% yield), m.p. 164-167 °C, ^{1}H NMR (d_6DMSO) 7.7-7.9 ppm (m,4H), 7.95 ppm (s,1H and s,1H); $(M+H)^+$ 170.

Example 2

1-(6-Bromonaphth-2-ylsulphonyl)-4-[4-(1-imidazolyl)benzoyl]piperazine

By an exactly analogous method to that described in Example 1, starting from 4-(1-imidazolyl)benzoic acid hydrochloride and 1-(6-bromonaphth-2-ylsulphonyl) piperazine was prepared 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(1-imidazolyl)benzoyl]piperazine (444mg, 85% yield), m.p. 207-209 °C (from ethanol/hexane), ^{1}H NMR (d_6DMSO) 3.0-3.2 ppm (broad s,4H), 3.5-3.8 ppm (broad s,4H), 7.1 ppm (s,1H), 7.4 ppm (d,2H), 7.6 ppm (d,2H), 7.75 ppm (s,1H), 7.8 ppm (t,2H), 8.2 ppm (t,2H), 8.3 ppm (s,1H), 8.4 ppm (s,1H), 8.45 ppm (s,1H), the spectrum also contained signals due to ethanol (<0.2 mol eq.); microanalysis, found: C, 55.0; H, 4.3; N, 10.4; S, 6.2 %; $C_{24}H_{21}N_4O_3BrS$ requires: C, 54.9; H, 4.0; N, 10.7; S, 6.1%; MS $(M+H)^+$ 525/527.

The requisite 4-(1-imidazolyl)benzoic acid starting material may prepared as described in J. Med. Chem. **33** 1091 (1990).

Example 3

1-(6-Bromonaphth-2-ylsulphonyl)-4-[4-(2-methylimidazol-4-yl)benzoyl]piperazine

By an exactly analogous method to that described in Example 1, starting from 4-(2-methylimidazol-4-yl)benzoic acid hydrochloride and 1-(6-bromonaphth-2-ylsulphonyl) piperazine was prepared 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(2-methylimidazol-4-yl)benzoyl]piperazine (423mg, 85% yield), m.p. 215-216 °C (from ethanol/hexane), ^{1}H NMR (d_6DMSO) 2.3 ppm (s,3H), 3.0-3.2 ppm (broad s,4H), 3.4-3.7 ppm (broad s,4H), 7.2 ppm (d,2H), 7.5 ppm (s,1H), 7.7 ppm (d,2H), 7.8 ppm (t,2H), 8.2 ppm (t,2H), 8.4 ppm (s,1H), 8.45 ppm (s,1H), 11.8 ppm (broad s,1H), the spectrum also contained signals due to ethanol (~0.33 mol eq.); microanalysis, found: C, 55.4; H, 4.8; N, 9.9; S, 5.8 %; $C_{25}H_{23}N_4O_3BrS$ requires: C, 55.6; H, 4.5; N, 10.1; S, 5.8%; MS $(M+H)^+$ 539/541.

The requisite 4-(2-methylimidazol-4-yl)benzoic acid starting material was prepared in an exactly analogous method to that described in Example 1, starting from 4-(2-methylimidazol-4-yl)benzonitrile, to give 4-(2-methylimidazol-4-yl)benzoic acid hydrochloride (913 mg, 94% yield), ^{1}H NMR (d_6DMSO) 2.6 ppm (s,3H), 7.95 ppm (d,2H), 8.05 ppm (d,2H), 8.15 ppm (s,1H); MS $(M+H)^+$ 203.

The requisite 4-(2-methylimidazol-4-yl)-benzonitrile starting material was prepared as follows. 4-Cyanophenacyl bromide (3.36g, 15 mmol) and acetamide (10 g) were stirred at 180 °C for 2 hrs. The reaction mixture was cooled and poured into water (50 ml); the suspension was filtered, and the filtrate extracted with ethyl acetate (3x50 ml) to give unwanted by-products (1.98 g, combined extracts and insoluble residue). The aqueous portion was basified with sodium hydroxide solution (20 ml of 1M) and re-extracted with ethyl acetate (1x100ml and 2x50 ml) to give product.This was purified by trituration with hot ethyl acetate to give 4-(2-methylimidazol-4-yl)-benzonitrile (838 mg, 31% yield), m.p. 240-241 °C, ^{1}H NMR (d_6DMSO) 2.3 ppm (s,3H), 7.7 ppm (s,1H), 7.75 ppm (d,2H), 7.9 ppm (d,2H), 12.0 ppm (broad s,1H); $(M+H)^+$ 184.

Example 4

1-(6-Bromonaphth-2-ylsulphonyl)-4-[4-(2-aminoimidazol-4-yl)benzoyl]piperazine

A solution of 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(2-t-butyloxycarbonylaminoimidazol-4-yl)benzoyl]piperazine (174 mg, 0.27 mmol) in dichloromethane (1 ml) and dioxan (4 ml) was treated with a solution of hydrogen chloride in dioxan (4 ml of 4M) and stirred overnight. The resulting solid was isolated by filtration to give crude product (163 mg); this was crystallised from ethanol to give 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(2-aminoimidazol-4-yl)benzoyl]piperazine (120mg, 77% yield), m.p. 274-275 °C, ^{1}H NMR (d_6DMSO) 3.0 - 3.1 ppm (broad s,4H), 3.3-3.7 ppm (broad s,4H), 7.35 ppm (d,2H), 7.45 ppm (s,3H), 7.65 ppm (d,2H), 7.8 ppm (t,2H), 8.2 ppm (t,2H), 8.4 ppm (s,1H), 8.45 ppm (s,1H); microanalysis, found: C, 48.8; H, 4.1; N, 11.8; S, 5.5 %; $C_{24}H_{22}N_5O_3BrS$. 1.0 HCl. 0.5 H_2O requires: C, 49.2; H, 4.1; N, 12.0; S, 5.5%; MS $(M+H)^+$ 540/542.

The requisite 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(2- t-butyloxycarbonylaminoimidazol-4-yl)benzoyl]piperazine starting material was prepared by a coupling method exactly analogous to that described in Example 1, starting from 4-(2-t-butyloxycarbonylaminoimidazol-4-yl) benzoic acid and 1-(6-bromonaphth-2-ylsulphonyl) piperazine, to give 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(2-t-butyloxycarbonylaminoimidazol-4-yl)benzoyl]piperazine as a colourless solid (after trituration with hot ethanol) (248 mg, 40% yield), m.p. 175-177 °C, ^{1}H NMR (d_6DMSO) 1.5 ppm (s,9H), 3.0-3.1 ppm (broad s,4H), 3.4-3.7 ppm (broad s,4H), 6.6 ppm (s,2H), 7.3 ppm (d,2H), 7.4 ppm (s,1H), 7.7 ppm (d, 2H), 7.8 ppm (t, 2H), 8.2 ppm (t,2H), 8.4 ppm (s,1H), 8.45 ppm (s,1H); MS $(M+H)^+$ 640/642 (w), $(M+H - 56)^+$ 584/585 (s), loss of C_4H_8.

The requisite 4-(2-t-butyloxycarbonylaminoimidazol-4-yl) benzoic acid starting material was prepared as follows. A stirred suspension of 4-(2-aminoimidazol-2-yl) benzoic acid hydrochloride (484 mg, 2.02 mmol) in triethylamine (3 ml) and dimethylformamide (3 ml) was treated with di-t-butyl dicarbonate (484 mg, 2.22 mmol) and the mixture stirred for ~72 hours. The solvent was removed *in vacuo* and water (20 ml) added to the residue; after

stirring for ~45 mins, the solid thus formed was isolated by filtration and washed with water to give 4-(2-t-butyloxycarbonylaminoimidazol-4-yl) benzoic acid (524 mg, 86% yield), m.p. >310 °C,

^{1}H NMR (d_6DMSO) 1.5 ppm (s,9H), 6.6 ppm (s,2H), 7.5 ppm (s,1H), 7.8 - 8.0 ppm (d,2H and d,2H); MS $(M+H)^-$ 302.

The requisite 4-(2-aminoimidazol-4-yl) benzoic acid starting material was prepared as follows. A solution of 4-(2-acetylaminoimidazol-4-yl) benzonitrile (540 mg, 2.39 mmol) was stirred at reflux temperature in aqueous hydrochloric acid (6 ml of 6M) for 16 hrs. The solution was cooled to 4 °C and left to crystallise for ~1 hr. The product was isolated by filtration, washed with aqueous hydrochloric acid (6M) and dried to give 4-(2-aminoimidazol-4-yl) benzoic acid hydrochloride (534 mg, 93% yield), m.p. >310 °C, ^{1}H NMR (d_6DMSO + D_2O) 7.5 ppm (s,1H), 7.7 ppm (d,2H), 7.95 ppm (d,2H); MS $(M+H)^-$ 204.

The requisite 4-(2-acetylaminoimidazol-4-yl) benzonitrile starting material may be prepared by a method exactly analogous to that given in J. Org. Chem. **59** 7299 (1994), starting from 4-cyanophenacyl bromide and N-acetyl guanidine, m.p. 269-271 °C, ^{1}H NMR (d_6DMSO) 2.05 ppm (s,3H), 7.5 ppm (s,1H), 7.75 ppm (d,2H), 7.9 ppm (d,2H), 11.2 ppm (broad s,1H), 11.8 ppm (broad s,1H); MS $(M+H)^+$ 226.

Example 5

1-(6-Chloronaphth-2-ylsulphonyl)-4-[4-(1*H*-6-oxopyridazin-3-yl)benzoyl] piperazine

To a solution of 4-(1*H*-6-oxopyridazin-3-yl)-benzoic acid (216mg, 1 mmol.) in dimethylformamide (5ml) was added 1-(6-chloronaphth-2-ylsulphonyl) piperazine (311mg, 1 mmol), 1-hydroxybenzotriazole (HOBT, 184 mg, 1.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride (EDAC, 230mg, 1.2 mmol), and the resultant suspension stirred overnight at ambient temperature. The solvent was removed *in vacuo*, the residue dissolved in dichloromethane, washed twice with water, dried and evaporated to give crude product (390mg). This was purified by flash chromatography using a Bondelute 10g silica cartridge, eluting with dichloromethane containing methanol (0 - 3%), giving essentially pure product. This was triturated with methanol to give1-(6-

chloronaphth-2-ylsulphonyl)-4-[4-(1*H*-6-oxopyridazin-3-yl)benzoyl] piperazine (231 mg, 45% yield), ^{1}H NMR (d_6DMSO) 2.8-3.2 ppm (broad s,4H), 3.4-3.8 ppm (broad s,4H), 6.95ppm (d,1H), 7.4ppm (d,2H), 7.5ppm (dd,1H), 7.55 ppm (m,3H), 8.0 ppm (d,1H), 8.15 ppm (d,1H), 8.25 ppm (m,2H), 8.5ppm (s,1H), 13.25ppm (broad s,1H); MS $(M+H)^+$ 509/511.

Example 6

Method A: The reaction is performed in a manner analogous to that described in **Example 5** using the appropriate starting materials.

Method B: To a solution of 1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(1H-6-oxopyridazin-3-yl)benzoyl]piperazine (510mg, 1 mmol) in dry dimethylformamide (5ml) was added sequentially bromoacetamide (152mg, 5.5 mmol), potassium carbonate (278mg, 2 mmol) and tetrabutylammonium carbonate (37mg, 0.1mmol) and the resultant mixture stirred at ambient temperature for 64 hours. Water (10ml) was added and the resultant precipitate collected, washed with water and dried to give essentially pure product (213mg) $(MH)^+$ 566/568 (1xCl). ^{1}H NMR (d_6-DMSO) 3.15ppm (s, 4H, under H_20), 3.55ppm (s, 4H), 3.73ppm (s,3H), 7.01ppm (d, 1H), 7.41ppm (d, 2H), 7.80ppm (d, 2H), 7.76ppm (d, 2H), 7.98ppm (s, 1H), 8.15ppm (dxd, 2H), 8.38ppm (s, 1H), 8.45ppm (s, 1H)

Method B (Alternative procedure): Where no precipitate was obtained the mixture was extracted with dichloromethane and the residue thus obtained purified by flash chromatography on a Jones FlashPack using a Bond Elut 20g silica cartridge, eluting with a dichloromethane containing methanol (0-5% gradient) giving essentially pure product. The starting material 1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(1H-6-oxopyridazin-3-yl)benzoyl]piperazine is **Example 5**

Method C: In a typical example excess methylamine gas (or other appropriate amine) was added to a solution of 1-(6-chloronaphth-2-ylsulphonyl)-4-[(6-methylsulphonylpyrimidin-4-yl)benzoyl]piperazine (or the 2-methylsulphonylpyrimidinyl isomer) in tetrahydrofuran or

similar appropriate solvent. The solution was stirred at ambient or elevated temperature until thin layer chromatography analysis indicated that the starting material had been consumed. The solution was concentrated *in vacuo* and the residue purified by column chromatography on silica. Where appropriate, the resultant free base was dissolved in 2:1 dichloromethane /methanol (20 mL) and treated with excess methanolic hydrogen chloride. The mixture was concentrated *in vacuo* to give the product as a near colourless foam, which could be crystallised, typically from aqueous ethanol.

In cases where the starting 1-(6-chloronaphth-2-ylsulphonyl)-4-[(6-methylsulphonylpyrimidin-4-yl)benzoyl]piperazine (or the 2-methylsulphonylpyrimidinyl isomer) is reacted with an alcohol, an excess of the alcohol starting material is used, either as the solvent or in an appropriate non-reacting solvent, and a base (typically DBU is added in slight excess). The reaction mixture is concentrated *in vacuo* and the residue purified by column chromatography on silica. Where appropriate, the resultant free base was dissolved in 2:1 dichloromethane/methanol (20 mL) and treated with excess methanolic hydrogen chloride. The mixture was concentrated *in vacuo* to give the product as a near colourless foam, which could be crystallised, typically from aqueous ethanol.

Method D: To a solution of 1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(2-*tert*-butyloxycarbonyl aminomethyl-pyridyl)benzoyl] piperazine (90 mg, 1.45 mmol) in tetrahydrofuran (2ml) was added ~4M methanolic HCl (2ml) and the resultant mixture stirred for four hours at ambient temperature. Removal of the solvent, after filtration, gave 1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(2-aminomethyl-pyridyl)benzoyl] piperazine (75mg, 1.35mmol).

Method E: To a solution of 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(6-chloropyridazin-3-yl)benzoyl]piperazine (500mg, 0.875 mmol) in DMPU (5ml) was added hydrazine hydrate (1ml) and the mixture heated at 80°C for 2 hours. The solvent was removed *in vacuo* and the resultant residue stirred vigorously with water (5ml) for 10 minutes, filtered, washed with water (10ml) then ethanol (10ml). The solid thus obtained was purified by HPLC on reversed phase silica eluted with 10-90% acetonitroile/water/0.1% triflouroacetic acid. Fractions

containing product were reduced and evaporated and the residue triturated with iso-propanol. There was thus obtained 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(6-hydrazinopyridazin-3-yl)benzoyl]piperazine as a pale yellow solid (107mg).

The requisite 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(6-chloropyridazin-3-yl)-benzoyl]piperazine was prepared as follows. To a solution of 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(1H-6-oxopyridazin-3-yl)benzoyl]piperazine (1.0g, 1.61 mmol) in phosphorus oxychloride (5ml) was added dry dimethylformamide (0.1ml). The resulting mixture was heated at 60°C for 4 hours then poured onto crushed ice and stirred vigorously for 30 minutes. The mixture was then extracted with dichloromethane (2x50ml) and the organic layer washed with saturated sodium bicarbonate then brine, dried over magnesium sulphate and evaporated to an off-white residue. This solid was stirred in hot methanol (10ml), allowed to cool and the off-white product filtered. There was thus obtained 1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(1H-6-oxopyridazin-3-yl)benzoyl]piperazine (620mg).

Method F: To a solution of 1-(6-chloronaphth-2-ylsulphonyl)-4-[(2-*tert*-butyloxypyrimidin-4-yl)benzoyl]piperazine (120mg, 0.213 mmol) in dichloromethane (5ml) was added a solution of hydrogen chloride in methanol (0.24 ml of ~4.5 M, 1.06 mmol). A precipitate formed immediately, and the reaction was stirred at ambient temperature for 1 hr. The solvent was removed *in vacuo* and the residue triturated with methanol. The solid was collected by filtration to give 1-(6-chloronaphth-2-ylsulphonyl)-4-[(2-hydroxypyrimidin-4-yl)benzoyl]piperazine hydrochloride as a colourless solid.

No	A	D	Method	MS: m/z	1H NMR (NMR, solvent)
1	1-hydroxy-6-dimethylamino-4-phenyl	6-chloro-2-naphthyl	A	$(M+H)^+$ 470/472.	^{1}H NMR (d_6DMSO) 2.7 ppm (s,6H), 3.0-3.2 ppm (broad s,4H), 3.4-3.8 ppm (broad s,4H), 4.2 ppm (s,2H), 7.05 ppm (d,1H), 7.4 ppm (d,2H), 7.6ppm (m,3H), 7.7-7.9 ppm (m,3H), 8.2 ppm (d,1H), 8.3 ppm (d,2H), 8.5 ppm (s, 1H), 9.5 - 10.2 ppm (broad s, 1H);
2	2-aminomethyl-4-pyridyl	6-chloro-2-naphthyl	D	521.3/523.4 $(M+H)^+$	^{1}H NMR (d_6DMSO) 2.95-3.20ppm (broad s, 4H), 3.40-3.80ppm (broad s, 4H), 4.20-4.33ppm (q, 2H), 7.43-7.50ppm (s,1H), 7.50-7.55ppm (s, 1H), 7.68-7.76ppm (dd, 1H), 7.76-7.93ppm (m, 4H), 8.03ppm (s, 1H), 8.14-8.22ppm (d, 1H), 8.22-8.32ppm (m, 2H), 8.50ppm (s 1H), 8.57-8.74ppm (m, 4H).
3	2-(N-(*tert*-butyloxycarbonyl)aminomethyl)-4-pyridyl	6-chloro-2-naphthyl	A	565.1/567.2 $(M+H)^+$	^{1}H NMR (d_6DMSO) 1.25 s(minor rot.)+1.35 s(major rot.)(9H);2.963.14 (broad s, 4H), 3.36-3.72ppm (broad s 4H), 4.20-4.24ppm (d 2H), 7.30-7.42ppm (m 1H), 7.42-7.50ppm (d 2H), 7.50-7.56ppm (m 2H), 7.64-7.76ppm (m 3H), 7.76-7.84ppm (dd, 1H), 8.10-8.20ppm (d, 1H), 8.20-8.30ppm (m, 2H), 8.48ppm (s, 1H), 8.50-8.56ppm (d, 1H).
4	2-methyl-1-imidazolyl	6-chloro-2-naphthyl	A	$(MH)^+$ 495/497 (1xCl)	^{1}H NMR (d_6-DMSO) 2.53ppm (s, 3H), 3.18ppm (broad s, 4H), 3.36ppm (s, 4H, under water), 7.59ppm (q, 4H), 7.72ppm (m, 2H), 7.82ppm (m, 2H), 8.16ppm (d, 1H), 8.27ppm (m, 2H), 8.52ppm (s, 1H), 14.8ppm (broad s, 1H)
5	2-methyl-1-imidazolyl	6-bromo-2-naphthyl	A	$(MH)^+$ 539/541 (1xBr)	^{1}H NMR (d_6-DMSO) 2.53ppm (s, 3H), 3.15ppm (s, 4H,), 3.56ppm (s, 4H), 7.57ppm (m, 5H), 7.71ppm (s, 1H), 7.80ppm (t, 2H), 8.14ppm (d, 2H), 8.36ppm (s, 1H), 8.44ppm (s, 1H)
6	2-amino-4-imidazolyl	6-chloro-2-naphthyl	D	496.4/498.3 $(M+H)^+$	^{1}H NMR (d_6DMSO) 2.88-3.14ppm (broad s 4H), 3.22-3.80ppm (broad s under H_2O 4H), 7.32-7.40ppm (d, 2H), 7.40-7.54ppm (m, 2.5H), 7.58-7.68ppm (d, 2H), 7.68-7.74ppm (d, 1H), 7.75-7.84ppm (d, 1H), 8.10-8.20ppm (d, 1H), 8.20-8.30ppm (d, 2H), 8.47ppm (s, 1H).

7	1-methyl-6-oxo-3-pyridazin-1(6H)-yl	6-bromo-2-naphthyl	A	$(MH)^+$ 566/568 (1xBr)	^{1}H NMR (d_6-DMSO) 3.15ppm (s, 4H, under H_20), 3.55ppm (s, 4H), 3.73ppm (s,3H), 7.01ppm (d, 1H), 7.41ppm (d, 2H), 7.80ppm (d, 2H), 7.76ppm (d, 2H), 7.98ppm (s, 1H), 8.15ppm (dxd, 2H), 8.38ppm (s, 1H), 8.45ppm (s, 1H).
8	1-carbamoylmethyl-6-oxo-3-pyridazin-1(6H)-yl	6-chloro-2-naphthyl	B	$(MH)^+$ 566/568 (1xCl)	^{1}H NMR (d_6-DMSO) 3.06ppm (s, 4H), 3.52ppm (s, 4H), 4.70ppm (s,2H), 7.14ppm (d, 1H), 7.18ppm (s, 1H), 7.42ppm (d, 2H), 7.56ppm (s, 1H), 7.70ppm (d, 1H), 7.79ppm (d, 1H), 7.84ppm (d, 2H), 8.03ppm (d, 1H), 8.16ppm (d, 1H), 8.24ppm (d, 2H), 8.47ppm (s, 1H)
9	1-(1-(methoxycarbonyl)methyl)-6-oxo-3-pyridazin-1(6H)-yl	6-chloro-2-naphthyl	B	$(MH)^+$ 581/583 (1xCl)	^{1}H NMR (d_6-DMSO) 3.04ppm (s, 4H), 3.52ppm (broad s, 4H), 3.70ppm (s, 3H), 4.94ppm (s,2H), 7.10ppm (d, 1H), 7.42ppm (d, 2H), 7.50ppm (d, 1H), 7.81ppm (d, 1H), 7.87ppm (d, 2H), 8.08ppm (d, 1H), 8.15ppm (d, 1H), 8.25ppm (d, 2H), 8.47ppm (s, 1H)
10	1-(2-(ureido)ethyl)-6-oxo-3-pyridazin-1(6H)-yl	6-chloro-2-naphthyl	B	$(MH)^+$ 595/597 (1xCl)	^{1}H NMR (d_6-DMSO) 3.04ppm (s, 4H), 3.39ppm (q, 2H), 3.54ppm (broad s, 4H), 4.13ppm (t, 2H), 5.39ppm (s, 2H), 6.00ppm (t, 1H), 7.02ppm (d, 1H), 7.42ppm (d, 2H), 7.71ppm (d, 1H), 7.81ppm (d, 1H), 7.90ppm (d, 2H), 7.99ppm (d, 1H), 8.16ppm (d, 1H), 8.26ppm (d, 2H), 8.47ppm (s, 1H)
11	1-(2-(acetamido)ethyl)-6-oxo-3-pyridazin-1(6H)-yl	6-chloro-2-naphthyl	B	$(MH)^+$ 595/597 (1xCl)	^{1}H NMR (d_6-DMSO) 1.71ppm (s, 3H), 3.06ppm (s, 4H), 3.43ppm (q, 2H), 3.56ppm (broad s, 4H), 4.14ppm (t, 2H), 7.02ppm (d, 1H), 7.42ppm (d, 2H), 7.71ppm (dxd, 1H), 7.81ppm (d, 1H), 7.86ppm (d, 2H), 7.94ppm (t, 1H), 8.02ppm (d, 1H), 8.16ppm (d, 1H), 8.24ppm (d, 2H), 8.47ppm (s, 1H)
12	1-(2-(dimethylamino)ethyl)-6-oxo-3pyridazin-1(6H)-yl	6-chloro-2-naphthyl	B	$(MH)^+$ 594/596 (1xCl)	^{1}H NMR (d_6-DMSO) 2.83ppm (s, 3H), 3.04ppm (s, 7H), 3.54ppm (broad s, 4H), 5.01ppm (s, 2H), 7.04ppm (d, 1H), 7.41ppm (d, 2H), 7.70ppm (d, 1H), 7.80ppm (d, 1H), 7.85ppm (d, 2H), 8.04ppm (d, 1H), 8.16ppm (d, 1H), 8.24ppm (d, 2H), 8.47ppm (s, 1H)
13	6-chloro-3-pyridazinyl	6-bromo-2-naphthyl	E	$(MH)^+$ 571/573/575 (1xCl, 1xBr)	^{1}H NMR (d_6-DMSO) 3.14ppm (s, 4H), 3.58ppm (s, 4H), 7.50ppm (d, 2H), 7.80ppm (d, 2H), 7.95ppm (d, 1H), 8.14ppm (m, 4H), 8.27ppm (d, 1H), 8.37ppm (s, 1H), 8.45ppm (s, 1H)

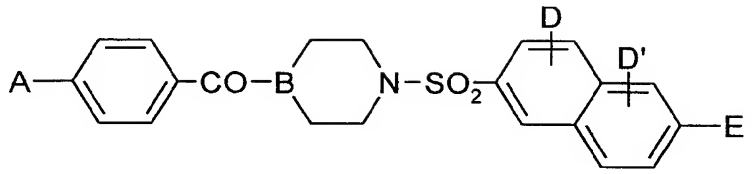
14	6-hydrazino-3-pyridazinyl	6-bromo-2-naphthyl	E	$(MH)^+$ 567/569 (1xBr)	^{1}H NMR (d_6-DMSO) 3.11ppm (s, 4H), 3.55ppm (s, 4H), 7.36ppm (d, 1H), 7.45ppm (d, 2H), 7.79ppm (d, 2H), 7.96ppm (d, 2H), 8.13ppm (t, 3H), 8.36ppm (s, 1H), 8.45ppm (s, 1H)
15	6-hydroxy-3-pyridazinyl	6-bromo-2-naphthyl	A	$(MH)^+$ 567/569 (1xBr)	^{1}H NMR (d_6-DMSO) 3.07ppm (s, 4H), 3.56ppm (broad s, 4H), 4.06ppm (s, 3H), 7.31ppm (d, 1H), 7.45ppm (d, 2H), 7.81ppm (t, 2H), 8.05ppm (d, 2H), 8.17ppm (t, 3H), 8.41ppm (s, 1H), 8.47ppm (s, 1H)
16	6-amino-3-pyridazinyl	6-bromo-2-naphthyl	A	$(MH)^+$ 552/554(1xBr)	^{1}H NMR (d_6-DMSO) 3.16ppm (s, 4H), 3.56ppm (s, 4H), 7.46ppm (d, 2H), 7.52ppm (d, 1H), 7.79ppm (d, 2H), 7.93ppm (d, 2H), 8.13ppm (d, 2H), 8.25ppm (d, 1H), 8.35ppm (s, 1H), 8.44ppm (s, 1H)
17	6-amidino-3-pyridazinyl	6-bromo-2-naphthyl	E	$(MH)^+$ 594/596(1xBr)	^{1}H NMR (d_6-DMSO) 3.15ppm (m, 4H), 3.59ppm (m, 4H), 7.45ppm (t, 3H), 7.80ppm (m, 2H), 8.08ppm (d, 2H), 8.14ppm (d, 2H), 8.28ppm (m, 6H), 8.43ppm (s, 1H)
18	6-methylamino-3-pyridazinyl	6-chloro-2-naphthyl	A	$(MH)^+$ 522/524(1xCl)	^{1}H NMR (d_6-DMSO) 2.35ppm (s, 3H), 3.15ppm (m, 4H), 3.58ppm (m, 4H), 7.46ppm (m, 3H), 7.66ppm (s, 1H), 7.82ppm (d, 1H), 7.95ppm (d, 2H), 8.10-8.24ppm (m, 4H), 8.45ppm (s, 1H)
19	2-((N-tert-butoxycarbonyl)amino methyl)-4-pyrimidinyl	6-chloro-2-naphthyl	A	622.5/624.5 $(M+H)^+$	^{1}H NMR ($CDCL_3$):1.45ppm (s, 9H), 2.90-3.30ppm (broad s, 4H), 3.40-4.10ppm (broad s, 4H), 4.58-4.68ppm (d, 2H), 5.68ppm (broad s, 1H), 7.38-7.47ppm (d, 2H), 7.53-7.64ppm (m, 2H), 7.72-7.79ppm (d, 1H), 7.87-7.97ppm (d, 3H), 8.05-8.13ppm (d, 2H), 8.30ppm (s, 1H), 8.70-8,78ppm (d, 1H)
20	2-((2-(dimethylamino)-N-ethyl)amino)-4-pyrimidinyl	6-chloro-2-naphthyl	C	579.5/581.5 $(M+H)^+$	^{1}H NMR (d_6DMSO) 2.75-2.87ppm (d, 6H), 2.95-3.19ppm (broad s, 4H), 3.19-3.33ppm (m, 2H), 3.33-3.84ppm (m, 6H), 7.25-7.35ppm (d, 1H), 7.40-7.50ppm (d, 2H), 7.57-7.70ppm (broad s, 1H), 7.70-7.78ppm (d, 1H), 7.78-7.86ppm (d, 1H), 8.07-8.23ppm (m, 3H), 8.23-8.31ppm (m, 2H), 8.40-8.47ppm (d, 1H), 8.47-8.52ppm (s, 1H), 10.20-10.40ppm (broad s, 1H)

21	2-dimethylamino-4-pyrimidinyl	6-chloro-2-naphthyl	C	536.7/538.7 $(M+H)^+$	^{1}H NMR (d_6DMSO)3.05-3.17ppm (broad s, 4H), 3.20ppm (s, 6H), 3.50-3.64ppm (broad s, 4H), 7.08-7.16ppm (d, 1H), 7.39-7.48ppm (d, 2H), 7.64-7.73ppm (d, 1H), 7.77-7.85ppm (d, 1H), 8.07-8.26ppm (m, 5H), 8.37-8.44ppm (d, 1H), 8.44-8.48ppm (s, 1H)
22	2-(N-(carboxymethyl) amino)-4-pyrimidinyl	6-chloro-2-naphthyl	C	566.7 (weak) $(M+H)^+$	^{1}H NMR (d_6DMSO)2.92-3.25ppm (broad s,4H), 3.25-3.95ppm (broad s, 4H under H_2O), 3.95ppm (s, 2H), 7.15-7.25ppm (d, 1H), 7.37-7.58ppm (m, 3H)m, 7.67-7.75ppm (d, 1H), 7.75-7.87ppm (d, 1H), 8.02-8.13ppm (d, 2H), 8.13-8.21ppm (d, 1H), 8.21-8.33ppm (d, 2H), 8.33-8.43ppm (d, 1H), 8.44-8.53ppm (s, 1H)
23	2-(2-(dimethylamino) ethoxy)-4-pyrimidinyl	6-chloro-2-naphthyl	C	580.1/582.3 $(M+H)^+$	^{1}H NMR (d_6DMSO) 2.85ppm (s, 6H), 2.92-3.20ppm (broad s, 5H), 3.20ppm (broad m, 5H under H_2O), 4.68-4.81ppm (m, 2H), 7.38-7.55ppm (d, 2H), 7.65-7.75ppm (d, 1H), 7.75-7.85ppm (m, 2H), 8.13-8.23ppm (m, 3H), 8.238.32(d, 2H), 8.48ppm (s, 1H), 8.67-8.75ppm (d, 1H), 10.30-10.50ppm (broad s, 1H)
24	2-aminomethyl-4-pyrimidinyl	6-chloro-2-naphthyl	D	522.6/524.6 $(M+H)^+$	^{1}H NMR (d_6DMSO) 2.90-3.22ppm (broad s, 4H), 3.22-3.90ppm (broad s, 4H under water), 4.30ppm (s, 2H), 7.45-7.57ppm (d, 2H), 7.68-7.78ppm (d, 1H), 7.78-7.87ppm (d, 1H), 8.03-8.13ppm (d, 1H), 8.13-8.22ppm (d, 1H), 8.22-8.31ppm (d, 2H), 8.31-8.40ppm (d, 2H), 8.52ppm (s, 1H), 8.52-8.68ppm (broad s, 3H), 8.89-8.97ppm (d, 1H)
25	2-ethoxy-4-pyrimidinyl	6-chloro-2-naphthyl	C	$(MH)^+$ 537/539(weak) (1xCl)	^{1}H NMR (d_6DMSO) 1.35 ppm (t, 3H), 2.9-3.2 ppm (broad s, 4H), 3.5-3.9 ppm (broad s, 4H), 4.4 ppm (q, 2H), 7.5 ppm (d, 2H), 7.7 ppm (m, 2H), 7.8 ppm (dd, 1H), 8.2 ppm (d, 2H and s, 1H), 8.3 ppm (s, 1H and s, 1H), 8.5 ppm (s, 1H), 8.7 ppm (d, 1H); the spectrum also contained signals due to ethanol (0.25 mol eq. and dichloromethane (0.25 mol eq.
26	6-dimethylamino-4-pyrimidinyl	6-chloro-2-naphthyl	A	$(MH)^+$ 536/538 (1xCl)	^{1}H NMR ($CDCl_3$) 3.10ppm (broad s, 4H), 3.35ppm (s, 6H), 3.44-3.95ppm (broad m, 4H), 6.71ppm (s, 1H), 7.47ppm (d, 2H), 7.62ppm (dd, 1H), 7.76ppm (dd, 1H), 7.88-7.99ppm (m, 3H), 8.08ppm (d, 2H), 8.33ppm (s, 1H), 8.77ppm (s, 1H)

27	6-aminomethyl-4-pyrimidinyl	6-chloro-2-naphthyl	D	$(MH)^+$ 522/524 (1xCl)	^{1}H NMR (d_6-DMSO) 3.08ppm (broad s, 4H), 3.30-3.85ppm (broad m, 4H), 4.23-4.32ppm (m, 2H), 7.53ppm (d, 2H), 7.74ppm (dd, 1H), 7.83ppm (dd, 1H), 8.14-8.33ppm (m, 6H), 8.50ppm (s, 1H), 8.67ppm (broad s, 3H), 9.29ppm (s, 1H)
28	6-amino-4-pyrimidinyl	6-chloro-2-naphthyl	C	$(MH)^+$ 508/510 (1xCl)	^{1}H NMR (d_6-DMSO) 3.05ppm (broad s, 4H), 3.25-3.85ppm (broad m, 4H), 7.00ppm (s, 1H), 7.66ppm (d, 2H), 7.74ppm (dd, 1H), 7.81ppm (dd, 1H), 7.89ppm (d, 2H), 8.18ppm (d, 1H), 8.27ppm (d, 2H), 8.50ppm (s, 1H), 8.66-8.92ppm (broad m, 3H)
29	6-methylamino-4-pyrimidinyl	6-chloro-2-naphthyl	C	$(MH)^+$ 522/524 (1xCl)	^{1}H NMR (d_6-DMSO) 3.01ppm (s, 3H), 3.14ppm (s, 4H), 3.58ppm (s, 4H), 7.07ppm (s, 1H), 7.52ppm (d, 2H), 7.69ppm (dd, 1H), 7.81ppm (dd, 1H), 7.96ppm (d, 2H), 8.12-8.27ppm (d, 3H), 8.45ppm (s, 1H), 8.66ppm (s, 1H)
30	2-hydroxy-5-pyrimidinyl	6-chloro-2-naphthyl	F	$(MH)^+$ 509	^{1}H NMR (d_6DMSO) 3.0-3.2ppm (broad s, 4H), 3.4-3.8ppm (broad s, 4H), 5.0-5.4ppm(br s,1H),7.4ppm(d,2H),7.7 ppm (d,2H), 7.75ppm (d,1H), 7.8ppm (d,1H), 8.15ppm (d,1H), 8.3ppm (d,1H and s,1H), 8.5ppm (s,1H), 8.8 ppm (s, 2H).

CLAIMS

1. A compound of formula (I)



(I)

wherein:

A is a 5- or 6-membered monocyclic aromatic ring containing 1 or 2 nitrogen ring heteroatoms optionally substituted by one, two or three atoms or groups selected from halo, oxo, carboxy, trifluoromethyl, cyano, amino, hydroxy, nitro, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino, di-C_{1-4}alkylamino or amino C_{1-4}alkyl;

the 1,4-phenylene ring of the compound of formula I is unsubstituted or is substituted by one or two substituents selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl, from the substituent $-(CH_2)_n Y^1$ wherein n is 0-4 and Y^1 is selected from hydroxy, amino, carboxy, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkylamino, di-C_{1-4}alkylamino, pyrrolid-1-yl, piperidino, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-C_{1-4}alkylpiperazin-1-yl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, C_{2-4}alkanoylamino, benzamido, C_{1-4}alkylsulphonamido and phenylsulphonamido, from the substituent $-(CH_2)_n Y^2$ wherein n is 0-4 and Y^2 is selected from carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl, N,N-di-C_{1-4}alkylcarbamoyl, pyrrolid-1-ylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, 1-oxothiomorpholinocarbonyl, 1,1-dioxothiomorpholinocarbonyl, piperazin-1-ylcarbonyl, 4-C_{1-4}alkylpiperazin-1-ylcarbonyl, C_{1-4}alkylsulphonamidocarbonyl, phenylsulphonamidocarbonyl and benzylsulphonamidocarbonyl, from a substituent of the formula $-X^3-L^2-Y^2$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^2-Y^2)$, $C(R^5)_2O$, O, $N(R^5)$ or $N(L^2-Y^2)$, L^2 is C_{1-4}alkylene, Y^2 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and from a substituent of

the formula $-X^3-L^3-Y^1$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^3-Y^1)$, $C(R^5)_2O$, O, $N(R^5)$ or $N(L^3-Y^1)$, L^3 is C_{2-4}alkylene, Y^1 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and wherein any heterocyclic group in a substituent of the 1,4-phenylene ring of compounds of formula I optionally bears 1 or 2 substituents selected from carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl and N,N-di-C_{1-4}alkylcarbamoyl, and wherein any phenyl group in a substituent of the 1,4-phenylene ring of compounds of formula I optionally bears 1 or 2 substituents selected from halo, trifluoromethyl, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy and C_{2-4}alkynyloxy;

B is CH or N;

the heterocyclic ring containing B is unsubstituted or is substituted by one or two substituents selected from hydroxy, oxo, carboxy and C_{1-4}alkoxycarbonyl; or one of the following:

$-(CH_2)_n-R$, $-(CH_2)_n-NRR^1$, $-CO-R$, $-CO-NRR^1$, $-(CH_2)_n-CO-R$ and $-(CH_2)_n-CO-NRR^1$;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R and R^1 are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl or where possible R and R^1 may together form a 5- or 6-membered optionally substituted saturated or partially unsaturated (preferably saturated) heterocyclic ring which may include in addition to the nitrogen to which R and R^1 are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur;

E is fluoro, chloro or bromo;

D and D^1 are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, oxo and hydroxy;

provided that when E is bromo and B is N then A is not 2-pyridyl, 4-pyridyl, 4-pyrimidinyl or 4-pyridazinyl, and when E is chloro and B is N then A is not 3-pyridyl, 4-pyridyl or 4-pyrimidinyl;

and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) as claimed in claim wherein A is a 5-membered monocyclic aromatic ring containing 1 or 2 nitrogen ring atoms.

3. A compound of formula (I) as claimed in claim 1 wherein A is pyrrolyl, imidazolyl or pyridazinyl ring.

4. A compound of formula (I) as claimed in claim 3 wherein A is 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyridazinyl, 3-pyridazinyl or 4-pyridazinyl.

5. A compound of formula (I) as claimed in claim 4 wherein A is 3-pyridazinyl, 1-imidazolyl or 4-imidazolyl.

6. A compound of formula (I) as claimed in any one of claims 1 to 5 wherein the 1,4-phenylene ring is substituted by carboxy, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl.

7. A compound of formula (I) as claimed in any one of claims 1 to 5 wherein the 1,4-phenylene ring is unsubstituted.

8. A compound of formula (I) as claimed in any one of claims 1 to 7 wherein the heterocyclic ring containing B is substituted by oxo, carboxy, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl.

9. A compound of formula (I) as claimed in any one of claims 1 to 7 wherein the heterocyclic ring containing B is unsubstituted.

10. A compound of formula (I) as claimed in claim 1 wherein:

A is imidazolyl;

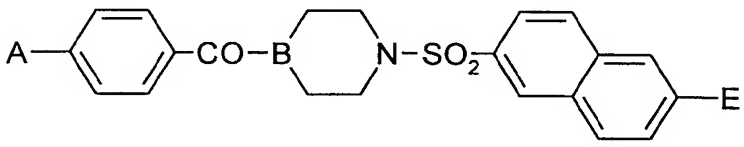
B is N;

E is chloro or bromo;

D and D^1 are both hydrogen.;

and pharmaceutically-acceptable salts thereof.

11. A compound of fomula (Ia):



wherein:

A is phenyl, pyrimidinyl (preferably 4-pyrimidinyl) or pyridyl (preferably 4-pyridyl) substituted (preferably at position 2- or 5-, in particular 5-, on the pyrimidinyl or pyridyl, and preferably at position 3- for phenyl) by one or two substituents selected from:

R^1-$(CH_2)_{1\ to\ 3}$-, RRN-$(CH_2)_{1\ to\ 3}$-, R-CO-, RRN-CO-, R-CO-$(CH_2)_n$-, RRN-CO-$(CH_2)_n$-, RRN-CO-RRN-$(CH_2)_n$-, RRN-RRN-$(CH_2)_n$- and R-O-$(CH_2)_n$-;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R is independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, N,N-di-C_{1-4}alkylaminoC_{1-4}alkyl;

R^1 is independently selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl, aminoC_{1-4}alkyl, N-C_{1-4}alkylaminoC_{1-4}alkyl, N,N-di-C_{1-4}alkylaminoC_{1-4}alkyl;

B is CH or N (preferably B is N);

D is bromo or chloro:

and pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 11 in association with a pharmaceutically-acceptable diluent or carrier.

13. A compound of formula (I) as defined in any one of claims 1 to 11 for use in medical therapy.

14. Use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined in any one of claims 1 to 11 in the preparation of a medicament for use in treating a Factor Xa mediated disease or medical condition.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/GB 99/01312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/32 A61K31/50 C07D207/34 C07D237/14 C07D237/12
C07D237/20 C07D237/24 C07D295/22 C07D213/56 C07D239/26
C07D239/42 C07D239/34 C07D239/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 28129 A (ZENECA LTD ;SMITHERS MICHAEL JAMES (GB); PRESTON JOHN (GB); STOCKE) 7 August 1997 (1997-08-07) claim 1 ---	1-14
A	WO 97 29104 A (ZENECA LTD ;FAULL ALAN WELLINGTON (GB)) 14 August 1997 (1997-08-14) claim 1 ---	1-14
A	WO 96 10022 A (ZENECA LTD ;FAULL ALAN WELLINGTON (GB); MAYO COLETTE MARIE (GB); P) 4 April 1996 (1996-04-04) claim 1 ---	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	13/08/1999

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INTERNATIONAL SEARCH REPORT

Inter...ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KUNITADA S ET AL: "FACTOR XA INHIBITORS" CURRENT PHARMACEUTICAL DESIGN, vol. 2, no. 5, 1 October 1996 (1996-10-01), pages 531-542, XP002057653 ISSN: 1381-6128 table 10 ---	1-14
A	WO 97 23212 A (DU PONT MERCK PHARMA) 3 July 1997 (1997-07-03) page 73; example 35 ---	1-14
P,X	WO 98 21188 A (TURNER PAUL ;PRESTON JOHN (GB); STOCKER ANDREW (GB); ZENECA LTD (G) 22 May 1998 (1998-05-22) the whole document ---	1-14
P,X	WO 98 54164 A (ITO FUMIO ;MORIYA NORIHIKO (JP); TAWADA HIROYUKI (JP); TAKEDA CHEM) 3 December 1998 (1998-12-03) see ex. 47-49,59-61,98,99,121,128,131,137,178,179, 183,191,194,209,235,257,258 ---	1-14
P,X	DATABASE WPI Section Ch, Week 9922 Derwent Publications Ltd., London, GB; Class B02, AN 99-263680 XP002110287 & WO 99 16747 A (DAIICHI PHARM CO LTD), 8 April 1999 (1999-04-08) abstract ---	1-14
P,Y	WO 99 06371 A (JAMES ROGER ;NOWAK THORSTEN (GB); WARNER PETER (GB); ZENECA LTD (G) 11 February 1999 (1999-02-11) claim 1 ---	1-14
P,Y	WO 99 16751 A (BERNOTAT DANIELOWSKI SABINE ;MERCK PATENT GMBH (DE); DORSCH DIETER) 8 April 1999 (1999-04-08) claim 1 -----	1-14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/GB 99/01312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9728129 A	07-08-1997	AU 1608597 A	22-08-1997
		EP 0880502 A	02-12-1998
WO 9729104 A	14-08-1997	AU 1553497 A	28-08-1997
		EP 0880516 A	02-12-1998
WO 9610022 A	04-04-1996	AT 168685 T	15-08-1998
		AU 696491 B	10-09-1998
		AU 3530795 A	19-04-1996
		BR 9509045 A	30-09-1997
		CA 2197471 A	04-04-1996
		CZ 9700893 A	16-07-1997
		DE 69503647 D	27-08-1998
		DE 69503647 T	14-01-1999
		EP 0783500 A	16-07-1997
		ES 2119472 T	01-10-1998
		HU 77769 A	28-08-1998
		JP 10506122 T	16-06-1998
		NO 971415 A	22-05-1997
		NZ 292983 A	23-12-1998
		PL 319430 A	04-08-1997
		SK 38597 A	10-09-1997
		ZA 9508085 A	24-04-1996
WO 9723212 A	03-07-1997	AU 1335897 A	17-07-1997
		CA 2240946 A	03-07-1997
		EP 0874629 A	04-11-1998
		HR 960597 A	30-04-1998
WO 9821188 A	22-05-1998	AU 4874897 A	03-06-1998
		NO 992230 A	07-05-1999
WO 9854164 A	03-12-1998	AU 7453498 A	30-12-1998
WO 9916747 A	08-04-1999	AU 9280698 A	23-04-1999
WO 9906371 A	11-02-1999	AU 8455798 A	22-02-1999
WO 9916751 A	08-04-1999	DE 19743435 A	08-04-1999
		AU 9540798 A	23-04-1999